UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/905,293	08/01/1997	MAE JOANNE ROSOK	030436.46SU1	5228

23914 7590 03/21/2005

STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 03/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/905,293	ROSOK ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-52* is/are pending in the application.

4a) Of the above claim(s) *23-27 and 32-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-22 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 12/06/04 in response to the non-final Office Action mailed 06/02/04. With this, Applicants amended the specification.

Status of Claims

2) Claims 1-6, 8-10, 12-14, 17 and 18 have been amended via the amendment filed 12/06/04.

Claims 1-6 and 8-52 are pending in the instant application.

Claims 1-6, 8-22 and 28-31 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Maintained

5) The objection to the drawings made in paragraph 6 of the Office Action mailed 08/14/02 and maintained in paragraph 7 of the Office Action mailed 06/02/04 is maintained for reasons set forth therein.

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 8 of the Office Action mailed 06/02/04 is withdrawn in light of Applicants' amendment to the specification.

Specification

7) The amino acid sequences recited in Figures 14, 18 and 19 contain more than four amino acids, yet are not identified by a SEQ ID NO. as required under 37 C.F.R 1.821 through 1.825. The amendment to page 6 of the specification filed 12/06/04 removes the sequence identifiers, SEQ ID NO: 10, SEQ ID NO: 22 and SEQ ID NO: 23, which were added via the amendment to the specification filed 02/23/1998. Any sequences recited in the instant specification which are encompassed by the definitions for nucleotide

and/or amino acid sequences as set forth in 37 C.F.R. 1.821(a)(1) and (a)(2) must comply with the requirements of 37 C.F.R 1.821 through 1.825. Note that branched sequences are specifically excluded from this definition.

APPLICANT MUST COMPLY WITH THE SEQUENCE RULES WITHIN THE SAME TIME PERIOD AS IS GIVEN FOR RESPONSE TO THIS ACTION, 37 C.F.R 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R 1.821(g).

8) The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP 608.01(o). Correction of the following is required: The limitation in the instant claims: 'multiple toxicity-associated regions' appears to lack antecedent basis in the specification. The limitation is supported in the original claim 4, but lacks antecedent basis in the instant specification. Amendment to the specification is suggested.

Rejection(s) Withdrawn

9) The rejection of claims 1-6, 8, 11, 13-15, 17-19, 21, 22 and 28-31 made in paragraph 17 of the Office Action mailed 05/12/03 and maintained in paragraph 11 of the Office Action mailed 0/02/04 under 35 U.S.C. § 102(e) as being anticipated by Yelton *et al.* (US 5,792,456, already of record), is withdrawn in light of Applicants' amendment to the claims and/or the base claims.

10) The rejection of claims 1, 3, 5, 12, 16 and 20 made in paragraph 18 of the Office Action mailed 05/12/03 and maintained in paragraph 12 of the Office Action mailed 06/02/04 under 35 U.S.C. § 102(b) as being anticipated by Gundel *et al.* (WO 93/02702, already of record), is withdrawn in light of Applicants' amendment to the claims and/or the base claims.

11) The rejection of claims 1, 2 and made in paragraph 13(a) of the Office Action mailed 06/02/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

12) The rejection of claim 8 made in paragraph 13(e) of the Office Action mailed 06/02/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

13) The rejection of claim 1 made in paragraph 13(f) of the Office Action mailed 06/02/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment

to the claim.

14) The rejection of claims 2-6 made in paragraph 13(g) of the Office Action mailed 06/02/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

15) The rejection of claims 1, 9 and 10 made in paragraph 16 of the Office Action mailed 06/02/04 under 35 U.S.C. § 102(b) as being anticipated by Suzuki *et al.* (JP 403128330A), is withdrawn in light of Applicants' amendment to the claims.

16) The rejection of claims 1-6, 8-22 and 28-31 made in paragraph 14 of the Office Action mailed 06/02/04 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is withdrawn upon further consideration. The limitation 'multiple toxicity-associated regions' has descriptive support in the original claim 4.

17) The rejection of claims 1-6, 8-12, 15, 16, 19, 20 and 28-31 made in paragraph 15 of the Office Action mailed 06/02/04 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s).

Rejection(s) Maintained

18) The rejection of claim 1 made in paragraph 13(b) and the rejection of claims 2-6 made in paragraph 13(c) of the Office Action mailed 06/02/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and herebelow.

Applicants submit that the recited amino acids 231-238 and 310-331 refer generically to the CH2 domain of an immunoglobulin molecule.

Applicants' argument has been carefully considered, but is not persuasive. Instant claims, as amended, recite that the administered immunoglobulin is modified by structurally altering multiple toxicity-associated regions, which 'consist' of amino acids 231-238 and 310-331 of the CH_2 domain. In order for one to locate these specific amino acids in a generic immunoglobulin, including a non-BR96 immunoglobulin such as an IgE, IgD, IgA etc., one has to know how to number the amino acids within the CH_2 domain and where exactly the numbering of amino acids starts within a specific sequence. This is particularly important in view of the disclosure at lines 10 and 11 of page 10 of the instant specification which vaguely refers to these regions as 'roughly localized to amino acids 231-238' and 'roughly localized to amino acids 310-331'.

How one should roughly localize amino acids 231-238 and 310-331 in generic immunoglobulins belonging to different classes, subclasses or isotypes is not understood. The rejection stands.

19) The rejection of claims 1-6 made in paragraph 13(d) of the Office Action mailed 06/02/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein. Whether or not the recitation 'a subject' recited in line 2 of the claims is the same as, or is intended to be different from 'a subject' recited at the end of line 1 and beginning of line 2 of the claims, is not understood. Applicants should consider providing proper antecedence to the second recitation.

New Rejection(s)

Applicants are asked to note the following new rejections made in this Office Action. These new rejections are necessitated by Applicants' amendments to the claim(s) previously not presented.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

20) Claims 1-6, 8-22 and 28-31, as amended, are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Base claims 1-6, as amended, include the new limitation: wherein multiple toxicity-associated regions 'consist of' amino acids 231-238 and amino acids 310-331 of said CH_2 domain. This new limitation is new matter because there is no descriptive support in the instant specification as originally filed for an immunoglobulin having a variable region and a constant region wherein the immunoglobulin is modified by structurally altering multiple toxicity-associated regions in the CH_2 domain, wherein the multiple toxicity-associated regions 'consist of' amino acids 231-238 and amino acids 310-331 of said CH_2 domain. Applicants have not pointed to a specific part of the specification that provides descriptive support for the above-identified new limitations. Lines 8-12 of page 10 of the instant specification describe the regions as 'roughly localized to amino acids 231-238' and 'roughly localized to amino acids 310-331'. Therefore, the added limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or to point

to specific pages and line numbers in the originally filed specification where support for such the above-identified new limitation can be found.

Rejection(s) under 35 U.S.C § 112, First Paragraph (Scope of Enablement)

21) Claims 1-6, 8-12, 15, 16, 19, 20 and 28-31, as amended, are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a method of inhibiting immunoglobulin-induced GI toxicity or gastroenteropathy, in animals such as dogs, comprising administering the CH_2-deleted BR96 IgG_3 monoclonal antibody, cBR96-A, said antibody produced by deleting the CH_2 domain of the constant region of the BR96 antibody, does not reasonably provide enablement for a method of inhibiting immunoglobulin-induced toxicity in any human or non-human subject comprising administering an immunoglobulin of any class or subclass, especially IgA, IgE, IgG2 or IgG4, which is structurally altered at multiple toxicity-associated regions that consist of amino acids 231-238 and 310-331 of the immunoglobulin's CH_2 domain, as claimed currently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

The instant claims are related to administering a generic immunoglobulin to a subject wherein the immunoglobulin comprises a variable region and a constant region and is modified by structurally altering multiple toxicity-associated regions in the CH_2 domain which consist of amino acids 231-238 and 310-331 wherein the administration inhibits immunoglobulin-induced toxicity in said subject. A review of the instant specification shows that the only modified immunoglobulin that has been administered to a canine subject for inhibiting immunoglobulin-induced acute gastroenteropathy is a BR96 IgG3 antibody which is deleted of the

CH_2 domain. See Example 3 and the section 'The Molecules of the Invetion'. However, outside this scope, the disclosure is not enabling for a method for inhibiting immunoglobulin-induced toxicity in any subject, human or non-human, comprising administering to the subject an immunoglobulin of any Ig class, subclass or isotype having mutations in the multiple toxicity-associated regions 'consisting' of amino acids 231-238 and 310-331 in its CH_2 domain, as recited currently. The description on page 7 of the specification, for example, describes the production of the BR96 monoclonal antibody having mutations at positions 235 and 237 (hBR96-2B); the BR96 antibody having mutations at positions 318, 320 and 32 (hBR96-2C); the BR96 antibody having a mutation at position 331 (hBR96-2D); and the BR96 antibody having mutations at positions 235, 237, 318, 320, 322 and 331 (hBR96-2H). There is no evidence that either the BR96 antibody or any other antibody including an IgA, IgE, IgG2 or IgG4, was indeed modified in the multiple toxicity-associated regions of its CH_2 domain said regions consisting of amino acids 231-238 and 310-331 as recited. Furthermore, there is no showing that such modified immunoglobulin consisting of mutations of amino acids 231-238 and 310-331 was administered to a human or non-human subject wherein the modified immunoglobulin inhibited immunoglobulin-induced toxicity in the subject. The state of the art indicates that several isotypes of antibodies, such as, IgE, IgA, human IgG2 and IgG4, do not cause ADCC or fix complement. For example, see lines 36-39 of Chang (US 5,872,222). However, these classes and subclasses of antibodies are currently encompassed within the scope of the claimed method (see especially claims 8 and 10). Secondly, with regard to those immunoglobulins other than IgE, IgA, human IgG2, IgG3 and IgG4 which do cause ADCC or fix complement, one cannot identify or locate the multiple toxicity-associated regions consisting of amino acid positions 231-238 and 310-331, because the instant specification does not provide adequate guidance as to where to start the amino acid numbering within the CH_2 region for each immunoglobulin class, subclass or isotype. This is critical because lines 7-15 of page 10 of the instant specification describes that the two toxicity associated domains are 'roughly localized' to amino acids 231-238 and 310-331. From the instant specification, one of skill in the art would not be able to make out how to accomplish this 'rough localization' in the absence of disclosure of a specific amino acid sequence of the CH_2 domain that is identified by a specific SEQ ID number. Which adjoining amino acids are precisely encompassed in this 'roughly localized' region cannot be envisaged. There is no exemplification of a single modified immunoglobulin belonging to a single class, subclass or isotype, including BR96, which contained deletion, insertion or substitution of a region that 'consisted' of amino acids 231-238 and 310-331, wherein

the modified immunoglobulin inhibited immunoglobulin-induced toxicity on administration to a human or non-human subject. Furthermore, there is not any evidence showing that identical mutations, if carried out in any immunoglobulin of any class or subclass other than BR96, at a region 'consisting of' amino acids 231-238 and 310-331 of the CH_2-domain, would result in a modified immunoglobulin that would prevent immunoglobulin-induced toxicity on administration to a subject, nor is such an inhibitory effect predictably obtained with any generic immunoglobulin. From the instant specification, it appears that the recited amino acid positions 'roughly localized' to 231-238 and 310-331 of the amino acid sequence of the CH_2 domain are pertinent or limited exclusively to the BR96 monoclonal antibody as depicted in some of the figures. Even with BR96, the modification did not involve amino acids 231-234, 236, 238, 310-317, 319, 321, 323-330. No evidence is of record showing that any other immunoglobulin other than the CH_2-deleted BR96 is indeed administered to a subject. There is neither a disclosure, nor any guarantee or predictability that if one administered to a subject, a non-BR96 antibody of any other class, subclass or isotype having mutations within the recited regions 'consisting' of amino acids 231-238 and 310-331 of the CH_2-domain, the resultant administration would automatically inhibit immunoglobulin-induced toxicity in the subject. No *in vivo* data, or correlative *in vitro* data are provided in the instant application, which show that the claimed method is operable with an immunoglobulin of any class/subclass or isotype having the recited structural alterations in the recited regions of the CH_2-domain. The immunoglobulin-induced toxicity-inhibiting effect cannot be predictably produced by the recited structural alterations in a generic immunoglobulin of any class/subclass or isotype, but requires a concrete demonstration of such an inhibitory effect in an acceptable *in vivo* animal model, or via *in vitro* experiments that are recognized in the art to correlate with the recited inhibitory effects. The instant specification lacks enabling disclosure in this regard. The full scope of the claims is not commensurate with the enabling disclosure. Due to the lack of specific disclosure and/or guidance, the lack of working examples enabling the full scope, the breadth of the instant claims, the unpredictability factor, and the quantity of experimentation necessary, undue experimentation would have been required at the time of the effective filing date of the instant application for one of ordinary skill in the art to reproducibly practice the full scope of the claimed methods. The ability to reproducibly practice the full scope of the claimed methods is well outside the realm of routine experimentation. The enablement (scope) provisions of 35 U.S.C. § 112, first paragraph, are not met and the claims are viewed as non-enabled with respect to their scope.

Remarks

22) Claims 1-6, 8-22 and 28-31 stand rejected.

23) **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

24) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of amendments, responses or papers is (571) 273-8300.

25) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

26) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

March, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER